NUTRITION REVIEWS

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FOOD AND NUTRITION: BASIC FACTORS IN INTERNATIONAL RELATIONS

At this period in the history of the world no one needs to be reminded that food is the most fundamental of human needs. In parts of Europe and Asia food is the first thought of millions of human beings when they wake up in the morning; craving for food accompanies them throughout the day and food is the subject of their uneasy dreams during the night. The destruction of food crops and food cargoes, the interruption to the normal transport of foodstuffs on land and sea, and the withdrawal of millions of farmers and farm laborers for service in the armed forces, have led to widespread starvation and undernutrition. Obviously, the first task of the United Nations, when the enemy is driven out of any country, will be to feed the hungry. No peace will have any meaning for these suffering millions, until their hunger is satisfied. The pledge of the United Nations to make stores of food available to the occupied countries as soon as hostilities cease is a political weapon of the first importance. The thought that bread and meat and milk will be available once more when the Axis is defeated must steel many a weary arm to carry on the struggle against the occupying forces. Hunger will lead to the greatest civil disorder in occupied countries when Axis forces are withdrawn unless arrangements are made for the immediate distribution of food.

The period between the first and second world wars was characterized by overproduction and underconsumption of food; of hunger in the midst of plenty. Huge food surpluses hung over world markets, threatening to destroy prices. Governments bought up and stored surpluses, raised tariff barriers against food imports, subsidized the restriction of production, and sometimes went to the length of destroying stores of food, such as meat, wheat, and coffee. At the same time the economic depression reduced buying power so that undernutrition and hunger prevailed while a market could not be found for abundant food supplies. Obviously something was wrong with such a civilization, and the outbreak of World War II was no surprise to those who fully understood the failure of governments to deal adequately with such economic and social problems. The need for international cooperation was emphasized by the lack of food in one country while its neighbor was trying desperately to get rid of unmarketable abundance, and the bankruptcy of governments was revealed by efforts to restrict food production while their people became undernourished.

The period between the two wars was also characterized by great advances in the science of nutrition and an awakening public consciousness of the needs and aspirations of the common man. Advances in nutrition clarified man's need for the protective foods and such food was comparatively expensive. Dietary studies here and in Great Britain showed that as income declined diets became less and less complete and as earnings rose more and more of the protective foods were purchased. Good and poor diets were found at every income level, but in general the level of income determined the adequacy of the diet.

Analysis of morbidity and mortality data showed that infant mortality, and the frequency and severity of illness varied directly with income. High standards of living were accompanied by low infant mortality, and

low frequency and severity of illness. In the best fed countries, where income was most equitably distributed and the highest standard of living prevailed, expectancy of life at 1 year of age, infant mortality, and the death rate from tuberculosis were the most favorable.

While many authorities in nutrition believe that too little is known of man's physiological need for the various nutrients, in no other field relating to human requirements is agreement more easily reached. A group of biochemists and physiologists convened by the League of Nations in 1935 agreed within three days on dietary standards. More recently a table of dietary allowances has been adopted by the Food and Nutrition Board of the National Research Council after wide consultation with authorities in Great Britain, Canada, and this country.

No matter what standard is adopted—those of the League of Nations, the British Medical Association, the British Ministry of Health, the Food and Nutrition Board, the Canadian Advisory Council on Nutrition, are cases in point—there is an enormous gap between diets actually consumed by the people in any country and the diets considered adequate by authorities in nutrition. In this country for example the following increases in production over the 1936 to 1940 averages would be required to provide diets for all coming up to the Food and Nutrition Board's table of daily allowances: meat 5 per cent, eggs 20 per cent, milk 80 per cent, citrus fruits and tomatoes 40 per cent, vegetables 180 per cent. Roughly corresponding but not comparable figures for Great Britain would be meat 30 per cent, eggs 55 per cent, milk 80 per cent, fruit 125 per cent, vegetables 90 per cent.

National economic policy between the two wars was not directly related to satisfying the physiological needs of the common man. Lack of security; fear of aggression—led to the attempt to achieve national self-sufficiency so as to be safe if war broke out. Wheat subsidies were common in European countries where wheat could not be raised so cheaply as on the prairies of Canada, Australia, and the United States of America. If, after the present war, governments decide on a policy of good nutrition for their people, self-sufficiency will become far too costly a policy. Foods will be purchased in the cheapest market so that there should be a healthy increase in the international trade and transport of foodstuffs.

Many farmers in this country and abroad remember the great slump in agriculture after the last war. It preceded and may have ushered in the world economic depression. The same thing will happen after this war, on a far greater scale, if an expanding market is not found for the present greatly increased agricultural production.

It is said that the production of food is the principal economic activity of man. Some 60 per cent of the world's working population is engaged in agriculture, and something like 90 per cent of agriculture is devoted to food production. Stabilization of agriculture throughout the world would do much to stabilize the whole economy. The adoption by governments, on a cooperative basis, of sound nutrition policies for their people, would provide an expanding market for agriculture for years to come. It would require the closest of international cooperation, and the establishment of specialized international agencies. Best of all would be its contribution to human welfare. For in the best sense of the words it would bring within measurable reach "Freedom from want . . . for all men everywhere in the world . . . attainable in our own day and generation."

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WHEAT PROTEINS

It is inevitable in wartime to find a shortage of meat and dairy products, our most valuable source of good protein. The possibility of extending the protein supply of the diet by more effective use of wheat has received consideration. The by-products of the milling of white flour not only are richer in iron and in the vitamins of the B-complex, but they also have a higher protein content. Would there be any advantage from the point of view of the proteins, if whole wheat flour were substituted for white flour? Two recent reports show conclusively that whole wheat flour is digested almost as completely as white flour, and that its proteins are of higher biologic value. There is thus no objection and some advantage in the substitution of whole wheat flour for white flour, but other considerations lead to the conclusion that such a step by itself will not solve the problem of maintaining the general protein content of the diet.

Krebs and Mellanby (*Lancet* **I,** *319 (1942)*) have studied the digestibility of white flour as compared to the national wheat meal flour of Britain and have reported that the former is slightly more digestible. They fed 6 men a diet of known composition which contained either from 480 to 700 g. of national wheat meal (85 per cent extraction) or white flour (75 per cent extraction) each day. About 90 per cent of the flour was eaten in the form of bread and the remainder in the form of puddings, sauces, and crackers. The feces were collected with the usual precautions for balance experiments and the dry weight and nitrogen content of these specimens were determined. The difference between the amount of material eaten and the amount in the feces is considered to be the amount which is digested and absorbed. This value, divided by the weight of ingested material and multiplied by 100, gives the percentage of digestibility. It is realized that the values obtained are minimal values because some of the material in the feces represents excreted substances.

For those persons who are interested in the details of dietary experiments it may be stated that the foods consisted of meat, fish, butter, oleomargarine, bacon, cheese, milk, potatoes, vegetables, and small quantities of rice and porridge. This basal diet supplied on the average 47 g. of fat, 71 g. of protein, and 272 g. of carbohydrate, or a total of 1795 calories daily. In addition to these basic foods unrestricted but measured quantities of bread and 1 pound of jam weekly were offered. The total caloric consumption averaged over 3000 calories daily. The experimental periods were of two weeks' duration.

In one series of these experiments it was found that 94 per cent of the dry matter and 89 per cent of the nitrogen of the national wheat meal were digested. In the case of white flour, 97 per cent of the dry matter was digested and, while no determinations of nitrogen were made, it was calculated on the basis of other data that the nitrogen utilization was about 91 per cent. The value for the digestibility of the dried weight of the food is an index of the utilization of the calories in the two types of flour and the value for the digestibility of nitrogen is an index of the utilization of protein in both products. It is evident from the results obtained that the differences in digestibility of these two types of flour are too small to be significant.

The biologic value of protein depends on the composition in terms of essential amino acids and at the present time this value can be measured only by means of animal experiments. The biologic value of the proteins in wheat flour has been again studied by Chick (*Lancet* **I,** *405 (1942)*) in England. Young rats were placed on diets in which the proteins were derived solely from white flour (73 to 75 per cent extraction), or national

wheat meal (85 per cent extraction), or whole wheat flour. These samples of flour all came from the same supply of wheat which was a blend of Canadian, English, and other wheats. The experimental diet contained adequate amounts of all known dietary essentials so that the protein alone was the limiting factor for growth. Particular care was exercised to give the animals enough B-vitamins in the form of yeast extract so that flour of higher extraction would have no effect on the outcome because of its greater vitamin content. To help assure this goal supplements of riboflavin and thiamine were added in the later weeks of the experiments. The growth rate was followed for a period of eight or nine weeks and for part of the time collection of the feces also was made. The experiments showed that 10.5 g. of the proteins of whole wheat were as useful to the rat as 13.1 g. of white flour proteins. Other arrangements of the data obtained, for example the calculation of the amount of protein in the food required for each gram of weight gained, showed that the biologic value of the proteins in whole wheat flour was superior to the biologic value of the proteins in white flour. The degree of digestibility was calculated, as in human experiments, by comparing the protein intake with the amount of nitrogen lost in the feces. It was found in two experiments that 87.9 and 86.8 per cent of the protein in white flour was digested and absorbed as compared to 85.4 and 86.6 in national wheat meal and 83.2 and 81.7 in whole wheat meal. These investigators pointed out that the slight difference in digestibility favoring white flour is more than compensated for by the greater biologic value of the national wheat meal or by the whole wheat meal in the promotion of growth. The growth of the animals fed on the experimental diets was not nearly so good as the growth of other animals on a diet containing casein as the source of protein. In other words, even the proteins of whole wheat are not biologically as good as the proteins of milk. Further, the animals receiving whole wheat meal and national wheat meal consumed more food than the animals receiving white flour. For example, in one series of experiments the animals receiving whole wheat meal consumed in a five week period 319 g. of food, those receiving national wheat meal consumed 276 g., and those receiving white flour 246 g. There are so many other data in the literature, and the differences in the results obtained in the present experiments are so great, that there is no doubt about the validity of the conclusions. When time permits, however, it would seem to be worth while to have similar studies made by means of the paired-feeding method, as described by Professor H. H. Mitchell of Illinois. The essential feature of this technic is that all the animals are restricted to the same quantities of food so that a much more accurate comparative study is made.

The chief point under discussion is not so much the comparative values of whole wheat and white flour but the nutritional value of the proteins of wheat and its various products as compared to the nutritional value of the best proteins for growth and maintenance, the proteins of milk and meat. While the proteins of wheat may not be in the same class with proteins from animal sources, they do represent a valuable contribution to the diet.

FLUORIDES AND SPINAL DEFORMITIES IN MAN

There is considerable controversy about whether small amounts of fluorine are markedly beneficial to the teeth but it is clearly established that larger amounts produce the condition known as mottled enamel. From animal experimentation it is known also that

skeletal changes can be produced by fluorides. This condition first became evident when rock phosphate, which may contain as much as 5 per cent of calcium fluoride, was substituted for bone ash in the feeding of pigs and dairy cattle some years ago.

Kemp, Murray, and Wilson (*Lancet* II, *93* (*1942*)) have been interested in determining whether skeletal changes in human beings might accompany dental fluorosis. A radiologic examination was made of the bones of persons in Oxfordshire, England, where mottled enamel is relatively common. The spine was selected for study. Many of these persons showed "round back" or kyphosis with restricted spinal movements. It is the belief of the investigators that the condition known as spondylosis deformans of older persons may be the result of progressive degeneration in the bones and further, that the changes might be prevented if the conditions which contribute to its development could be learned.

Examinations of 5 adults and 22 children were made. It was found that disturbances of natural ossification were fairly common among the children but there was no definite evidence that fluorides were responsible. However, 6 children with severe mottled enamel all showed disturbances of ossification, and persons with severe skeletal changes had extensive damage to their teeth. The authors believe that their observations are in accord with clinical experiences and suggest that spondylosis deformans results from progressive degeneration and malformation during youth. Fluorides in drinking water and soil, in association with defective diet, may favor such malformation. Skeletal changes associated with dental fluorosis have been reported in India and South Africa but no similar observations have been reported heretofore in America or Great Britain. Obviously more experimental work and extensive observational studies are needed before the significance of fluorides in the food and drinking water can be evaluated even to a reasonable degree. The limited observations of the authors are scarcely more than suggestive.

DIETARY FAT AND FATTY LIVERS

Infiltration of fat into the liver has been a fascinating and baffling problem to the pathologist for a considerable time. During the last decade chemists have interested themselves in studying this condition and its cause. Hershey and Soskin as early as 1931 (*Am. J. Physiol.* **98,** *74* (*1931*)) showed that in the depancreatized dog infiltration of fat into the liver occurred more readily when a saturated fat was fed in contrast to an unsaturated fat. Later Channon and Wilkinson (*Biochem. J.* **30,** *1033* (*1936*)) demonstrated that liver fat infiltration depended directly upon the intake of the C_{14} to C_{18} saturated fatty acids (iodine no. 0), with the single exception of coconut oil which is slightly unsaturated (iodine no. 10). The amount of fat deposited in the liver varied inversely with the iodine value. Butter (iodine no. 33) caused six times more fat deposition in the liver than cod liver oil (iodine no. 145).

These authors used a variety of fats and oils in their previous work, and it is not clear whether inadequate choline was the cause of the fatty livers, since choline has a lipotropic action, or whether the physical properties of the fats were responsible for the differences found between the saturated and the unsaturated fatty acids. These authors have now studied (*Biochem. J.* **36,** *214* (*1942*)) the effects of progressive hydrogenation of a single oil, and the effects of fats containing solid unsaturated acids upon the fat deposition in the liver.

Linseed oil was selected for study since it is composed almost entirely of C_{18} acids, most of which are unsaturated (iodine no.

175). The oil was progressively hydrogenated and fed to experimental rats in groups of 10, in a series of experiments. In the first experiment 5 groups of animals were fed for fourteen days on 40 parts of linseed oil meal, or hydrogenated linseed oil meal whose iodine numbers were 142, 123, 90, and 55, respectively. The protein was furnished by caseinogen and vitamins A and D as concentrates. The second and third experiments were made for the purpose of determining the effect of the physical state of the fat upon fat infiltration of the liver. Beef drippings, olive oil, olive oil plus elaidin at several different levels, and olive oil plus tristearin or plus triolein were used. At the end of the experimental period the rats were sacrificed and fatty acids prepared from the carcass as well as from the liver. In the second and third experiments omental and perirenal fats only were used to represent carcass fats. The saturated acids, solid unsaturated acids, and liquid unsaturated acids were then determined. The daily intakes and excretions of the various groups were not controlled but were not significantly different.

A comparison of the effects of the liquid unsaturated acids, solid unsaturated acids, and solid saturated acids on liver fat deposition indicated that the degree of liver fat infiltration was related to the proportion of C_{14} to C_{18} saturated fatty acids. This held for the diets high in fat and low in choline. Solid unsaturated acids exerted no such effect. Elaidic acid appeared in the liver, carcass, and fecal fat in proportions depending upon the amounts present in the diet.

This series of experiments emphasizes in a striking manner the influence of the type of fat upon the accumulation of fat in the liver of the rat. The results show that the ingestion of excessive amounts of edible saturated fats and oils is contraindicated. This applies particularly to acquired food habits and tastes of peoples. Further, the use of these same fats by individuals with hepatic disorders should be reduced to a minimum. In previous work butter was shown to cause a comparatively heavy deposition of fats in the liver. On the basis of these results this food item would also come in for some criticism. Several factors must be kept in mind in evaluating this work. First the data presented in this report would be greatly enhanced if they were accompanied by histopathologic studies. It is not uncommon to find relatively high concentrations of fat in the rat liver, as much as 20 per cent, without microscopic evidence of cellular pathology. The highest values recorded in Channon's work according to his liver analyses were only 24 g. of liver fat per 100 g. of fresh liver tissue. It is possible in the light of these facts that Channon's chemical data which indicate fat accumulation in the liver, and presumably an undesirable or even pathologic state, are not truly indicative of structural damage. Therefore, unless definite signs of cellular pathology can be shown to accompany the increased deposition of fat as the result of the dietary fat ingestion, there is little cause for immediate concern.

HISTIDINE, HISTAMINE, AND TOXEMIA OF PREGNANCY

Some evidence has accumulated in recent years to indicate that the normal metabolism of the amino acid histidine may be impaired in pregnancy. Histidinuria is a normal characteristic of pregnancy in the human being and urinary excretion of histidine ranges between 15 and 50 mg. per cent. Histidinuria is not appreciably affected in cases of mild or preeclamptic toxemia, but it is greatly diminished or absent in patients with serious symptoms of preeclamptic toxemia of pregnancy. The

histaminase activity of the blood of pregnant women is greatly increased over that of nonpregnant women. It appears from these facts that there is evidence for associating severe toxemia of pregnancy with abnormal histidine and histamine metabolism.

In a recent report by Kapeller-Adler (*Biochem. J.* **35,** *213 (1941)*) further evidence has been obtained to show that histidine metabolism is disturbed in preeclamptic toxemia. Fifty-eight cases of toxemia of pregnancy were examined. The study showed that histidinuria is not appreciably affected in patients with mild toxemia, but is considerably reduced or absent in patients with severe symptoms of preeclamptic toxemia. The author considers this diminution in histidine excretion to be so constant that it is useful as a diagnostic sign of severe toxemia of pregnancy. The urine from 6 patients with severe toxemias was used to isolate histamine as either the histamine picrate or flavinate. The urine from these patients yielded several milligrams of histamine. No histamine was isolated from the urine of patients with a normal pregnancy. The methods of preparation are at best approximate and it is to be expected that only a fraction of the total histamine was isolated. Kapeller-Adler considers the origin of histamine to be from the amino acid histidine. He believes that tissues of human beings, especially the kidneys, like the tissues of experimental animals, contain an enzyme which converts histidine to histamine by decarboxylation. Such an enzyme, histidine decarboxylase, has been reported by Werle to be present in animal tissues, especially the kidney. It is more effective in the absence of oxygen than in the presence of it. On the other hand, the enzyme histaminase, first described and isolated by Best, is also present in many tissues, especially kidney, and destroys histamine; this enzyme is effective only in the presence of oxygen. Werle further claims that the activity of these enzymes, histidine decarboxylase and histaminase, is dependent not only upon the presence or absence of oxygen but probably far more upon the presence of various unknown inactivators which regulate their activity. The gonadotropic hormones may fall in this class since there is apparently some relationship between the excretion of histidine and that of gonadotropic hormones in pregnancy of human beings. Thus it is assumed that the amount of histamine excreted is dependent upon the relative activity of these two enzymes, one of which forms histamine while the other destroys it.

The author does not point out the general fact that in severe toxemia of pregnancy very little urine may be excreted and that with reduction of urinary volume many normal urinary constituents are reduced, particularly when there is an albuminuria. It is possible that part of the diminution in urinary histidine is a result of decreased urine volume. It would be interesting to know whether histamine is found only in cases with marked albuminuria. However, the observations may be of clinical importance in view of the fact that the histidine and histamine concentrations in the body are in part dependent upon the diet. As early as 1935 Kapeller-Adler showed that the excretion of histidine in the urine was directly dependent upon the dietary intake. Protein-rich diets and particularly meat proteins caused the excretion of more than double the normal histidine output of pregnancy. Reducing the meat protein of the diet caused a marked reduction in the excretion of histidine in the urine. Purine-rich diets were intermediate in this respect.

A consideration of these facts together with the possibility that dietary histidine may be the direct source of the histamine observed in these experiments might be interpreted to mean that a diet low in histidine would be of value in the treatment of toxemias of pregnancy. In fact such diets, low in meat and eggs, have often been prescribed for pregnant women. However in a recent paper Burke has said that: "We can

say with certainty, today, that there is no satisfactory evidence that a liberal intake of protein is a cause of toxemia" (*J. Am. Dietet. Assn.* **17,** *102 (1941)*). Furthermore, Strauss (*Am. J. Med. Sci.* **195,** *723 (1938)*) believes that liberal protein allowances of 100 g. per day may actually decrease the incidence of toxemia of pregnancy. The excretion of histidine observed in pregnancy may also be interpreted as indicating an increased requirement for this amino acid because of this loss during pregnancy. Thus, without definite evidence to the contrary, it would seem unwise to limit the intake of any dietary essential, particularly protein, during pregnancy.

ASCORBIC ACID AND PHOSPHATASE ACTIVITY

A reduction in serum alkaline phosphatase has been observed both in guinea pigs maintained on a diet low in vitamin C and in infants suffering from scurvy. Tests *in vitro* have indicated that ascorbic acid does not itself activate alkaline phosphatase. A recent study has been reported by Schwachman and Gould (*J. Nutrition* **23,** *271 (1942)*) showing the differences in serum alkaline phosphatase in guinea pigs fed a normal diet, the same diet plus extra ascorbic acid, a vitamin C deficient diet, and finally those fed the deficient diet plus different amounts of pure ascorbic acid.

Tests with guinea pigs 6 to 7 weeks old indicated that the scurvy-producing diet was adequate for normal growth and development when supplemented by sufficient ascorbic acid. Without such supplement, the animals showed evidence of scurvy in eighteen to twenty-four days. The phosphatase determinations were made on blood drawn directly from the heart of animals under light ether anesthesia.

The Schwachman modification of the Bodansky method was used for alkaline serum phosphatase. The method of Fiske and SubbaRow was used for acid soluble inorganic phosphate. Gutman and Gutman's method for serum "acid" phosphatase was used.

Six groups of 5 guinea pigs each were used in the experiments. Two groups received no ascorbic acid, one group received 1 mg. daily, one group received 6 mg. daily, one group received soybean chow supplemented with fresh vegetables, and the last group was given the vegetable diet plus ascorbic acid. During the first five days the alkaline phosphatase value of all except the groups receiving vegetables decreased, presumably because the animals failed to eat the scurvy-producing diet. After the animals began to eat, the serum values increased in animals receiving ascorbic acid supplements but continued to decrease in the animals receiving no supplement. The addition of 1 mg. of ascorbic acid sufficed to maintain practically the same serum phosphatase level as did 6 mg., although signs of scurvy appeared in some animals at the 1 mg. level. Older guinea pigs deprived of vitamin C also showed a decrease in alkaline phosphatase activity, indicating that this phenomenon is not characteristic of young animals only.

In order to ascertain whether factors other than the vitamin C content of the diet were involved, rabbits were fed the scurvy-producing diet and compared with others on the regular diet. Rabbits do not develop scurvy and apparently synthesize their own vitamin C. No significant difference in rabbit serum alkaline phosphatase appeared, when rabbits receiving the scurvy-producing diet were compared with those receiving the regular diet.

The question of whether an enzyme activator is lacking or an inhibitor is present in the tissues of scorbutic guinea pigs appeared to be answered in the negative by the purely

additive property of sera of high and low alkaline phosphatase activity. Changes in the diet from high to low vitamin C content had no effect on the serum "acid" phosphatase or on serum inorganic phosphate.

Finally, 55 guinea pigs were kept on the scurvy-producing diet for eighteen to twenty days when clinical signs of scurvy were apparent. The administration of ascorbic acid to these animals resulted in a prompt increase in alkaline phosphatase. Removal of the supplement then resulted in a prompt lowering of the values. The increases observed were practically independent of the dosage. The results suggest that ascorbic acid stimulates alkaline phosphatase production rather than serving as an activator to the existing alkaline phosphatase.

B-VITAMINS AND NEUROPATHOLOGY

Neurologic manifestations invariably accompany dietary deficiencies of the vitamin B-complex and the signs vary in experimental animals from ataxia to convulsive seizures. Evidence of nerve disorders are common in such diseases as chronic alcoholism, pernicious anemia, pellagra, and sprue. Early attempts to isolate the dietary factors involved centered about thiamine, and many workers consistently maintain that a lack of thiamine results in histopathology of the peripheral nerves. On the other hand, many able investigators, using a variety of species, have shown under good experimental conditions that an acute thiamine deficiency does not invariably result in recognized neuropathology. There is a vast amount of evidence to show that the administration of thiamine to an animal acutely deficient in thiamine causes a dramatic and prompt remission of the neurologic signs within a period of minutes, and complete recovery within a few hours.

In considering pathologic changes in nutritional disorders one must consider the time factor. It takes a certain time for pathologic changes to develop to the state where they may be recognized. In acute deficiencies experimentally produced in a short time it is probable that functional changes resulting in clinical signs will be evident before pathologic changes are detectable. However, in chronic deficiencies, produced over a longer period of time, it is usual that pathologic lesions are demonstrable when definite clinical signs are observed. This certainly seems to be the case in thiamine deficiency.

Attempts to identify other dietary factors that are involved in the production of neuropathology have recently been made. Phillips and Engel (*J. Nutrition* **16**, *451* (*1938*)) demonstrated that diets low in riboflavin caused pronounced degeneration of the myelin of the main peripheral nerve trunks in the growing chick and concluded that riboflavin was associated with myelin metabolism. The same authors (*J. Nutrition* **18,** *227* (*1939*)) presented evidence to show that pantothenic acid was likewise essential for the prevention of neuropathology of the spinal cord of the chick. In attempts to show neuropathology in the rat fed a low riboflavin diet, early experiments were entirely negative; however, when a more highly purified diet was used, Shaw and Phillips (*J. Nutrition* **22,** *345* (*1941*)) demonstrated a variety of pathologic changes as the result of a riboflavin deficiency in the rat, and some of these changes involved both peripheral nerves and the spinal cord. Thus it has been shown that a deficiency of factors of the B-complex other than thiamine cause neuropathology.

Wintrobe, Miller, Follis, Stein, Mushott, and Humphreys (*J. Nutrition* **24,** *345* (*1942*)) have now shown that in certain experimental conditions calcium pantothenate and pyridoxine prevent sensory neuron degeneration in the growing pig. Wintrobe, Miller, and

Lisco (*J. Exp. Med.* **68,** *207 (1938)*) had previously reported abnormal gait and pathologic changes in the nervous system of pigs as the result of feeding an inadequate diet. The diet contained ample thiamine, riboflavin, nicotinic acid, and vitamins A, D, and E. Obviously the deficiency factor expressing itself under these experimental conditions was still unrecognized. By using a highly purified diet Wintrobe and coworkers in the present report studied the lack of the individual vitamins, thiamine, riboflavin, nicotinic acid, pyridoxine, choline, calcium pantothenate, and vitamin A. They found that sensory neuron degeneration occurred in 41 growing pigs when either pyridoxine or pantothenic acid or both were lacking from the diet. When both of these vitamins were fed, degenerative changes did not occur once among the 26 control pigs.

Other observations were made. A subacute inflammation of the colon occurred when the diet was inadequate in pantothenic acid. The elimination of pyridoxine from the ration resulted in epileptiform fits and anemia. These could be cured promptly by administration of pyridoxine. The authors could not demonstrate histologic changes in the nervous system as the result of a thiamine deficiency although signs of thiamine deficiency were in evidence. Choline likewise did not appear to be involved in these experiments in the maintenance of nerve structure. When no pyridoxine was included in the diet fatty livers developed. Previously choline had been shown to prevent fatty livers and now these authors were able to demonstrate that fatty livers in the pig developed not only in the absence of choline from the diet but also in the absence of pyridoxine.

It might be that this study does not fully eliminate the possibility that riboflavin is concerned with nerve histopathology. It is extremely difficult to demonstrate some of these deficiencies in the young of mammals because of the comparatively long nursing period. During this time enough riboflavin is ingested to form and develop the nervous system adequately. Only under the most stringent dietary regimen will some of these deficiencies appear. On the other hand, these authors seem to have eliminated many of the possibilities for the occurrence of such a case, in that they were able to eliminate entirely the signs and pathology by feeding pyridoxine and pantothenic acid.

This work further substantiates the involvement of factors of the B-complex other than thiamine in the normal functioning of the nervous system. The results are also interesting in relation to the recent report of Scudi and Hamlin (*J. Nutrition* **24,** *273 (1942)*). These authors studied the blood lipids in 27 pantothenic acid deficient dogs of different age groups and found that a pantothenic acid deficiency developed sooner in weanling than in adult dogs. The deficient dogs showed a decrease in cholesterol, cholesterol ester, lipoid phosphorus, and total lipids. The addition of pantothenic acid to the diet brought about an immediate rise in the lipid concentrations of the blood. In the deficient dogs the livers became extremely fatty; this condition was only partially corrected by the addition of pantothenic acid. The levels of choline and pyridoxine fed appear to be adequate.

The work of Scudi and Hamlin offers in part an explanation for the neuropathology in pantothenic acid deficient pigs in so far as the disturbance in lipid metabolism may be reflected in the neuropathologic signs.

CITRUS FRUIT JUICES AND CALCIUM ASSIMILATION

In 1939 Lanford (*J. Biol. Chem.* **130,** *87 (1939)*) reported experiments which showed that the addition of moderate amounts of orange juice to a wheat-milk diet

increased the calcium assimilation of the rat. This series of experiments raised the important question as to whether the citric acid and citrates were responsible for this effect. Lanford has sought an answer to this problem in a study of the effect of large doses of citric acid and potassium citrate mixtures upon growth and calcium assimilation (*J. Nutrition* **23,** *293* (*1942*)). The assumption that citric acid or citrates favorably influences calcium assimilation is not without some support, according to the author, since other investigators have reported beneficial effects of citric acid-citrate mixtures on experimental as well as clinical rickets and even in some cases on bone ash.

Rats were fed a basal diet of 5 parts ground wheat and 1 part of dried whole milk plus sodium chloride. This diet was reported to contain about .02 per cent citric acid. Daily supplements of citric acid-potassium citrate containing 1.6 per cent free and combined citric acid were fed. The results show that this supplement of citric acid-potassium citrate which is approximately equivalent to 10 ml. of fresh orange juice daily, increased the rate of growth and the total calcium retention of young rats. Unlike orange juice, which was previously studied in a similar way, it had no appreciable effect on the percentage of the dietary calcium which was retained in the body of the growing animal. From these results and previous studies it would seem that orange juice contained some substance in addition to its content of citric acid and citrates which favored calcium assimilation in growth of the rat fed a whole wheat-dried milk diet.

This report merits attention in that it indicates that orange juice furnished a factor or factors which effected an increased efficiency in the assimilation of calcium. There is no hint as to its nature. Several possibilities present themselves. Orange juice contains appreciable quantities of provitamin A, vitamin C, and no doubt some members of the vitamin B-complex. A diet minimal in any one of these might affect the digestive and absorptive powers of the gastrointestinal tract thus limiting the assimilation of calcium. The addition of orange juice might conceivably raise the dietary minimal intakes of some of these factors to more nearly optimum levels and thus bring about a more favorable calcium assimilation.

CARDIAC FAILURE IN CHRONIC THIAMINE DEFICIENCY

Heart failure occasionally occurs in patients with beriberi. It has been observed both in the naturally occurring disease and in patients who develop thiamine deficiency as a result of addiction to alcohol. In these individuals the heart is tremendously dilated and edema is massive. Administration of thiamine causes prompt decrease in cardiac size and produces dramatic relief of symptoms. Weiss and Wilkins (*Ann. Int. Med.* **51,** *104* (*1937*); *J. Am. Med. Assn.* **115,** *832* (*1940*)), in their attempts to determine the cause of the cardiac decompensation, observed that venous pressure was elevated in only some of their patients, circulation time was decreased, and the difference between the oxygen content of arterial and venous blood was less than normal. Two Japanese investigators, Hayasaka and Inawashiro (*Tohoku J. Exp. Med.* **12,** *29* (*1928*)), had previously concluded that the cardiac output in beriberi is increased. These results indicate that there is an increase in the velocity of blood flow in patients with cardiac decompensation caused by thiamine deficiency. The circulatory dynamics, therefore, must be distinctly different in this form of heart failure from that in the types ordinarily seen, because the velocity of blood flow is usually decreased, circulation time

increased, venous pressure elevated, and arteriovenous oxygen difference exaggerated. Physicians and physiologists alike, therefore, welcome the report of Porter and Downs (*Ann. Int. Med.* **17,** *645 (1942)*) which confirms the observations of Weiss and Wilkins and attempts to explain the circulatory abnormality in patients with beriberi heart.

The 2 men studied by Porter and Downs were critically ill at the time of their admission to the hospital. Both were addicted to alcohol and both recovered dramatically from the manifestations of heart failure when they were given thiamine. The evidences they showed of congestive cardiac decompensation were elevated venous pressure, dependent pitting edema, reduction in vital capacity, cardiac dilatation, and pulmonary congestion (x-ray). In neither case could the edema be attributed to hypoproteinemia. During the period of decompensation, circulation time was decreased, cardiac output increased, and arteriovenous oxygen difference diminished. Coincident with recovery induced by thiamine there was a change toward normal in each of these measurable circulatory phenomena. In one patient, plasma and total blood volume were increased. The oxygen consumption of both patients was originally greater than normal, but interpretation of these results is complicated by the fact that therapy was begun before initial determinations were made. The heart shadows, as measured roentgenologically, began to decrease in size within a few days after institution of therapy and returned to normal limits within two weeks. Porter and Downs agree with Weiss and Wilkins that the most satisfactory explanation for the altered circulatory dynamics in patients with beriberi heart is that there is a failure of the myocardium and an increase in the volume of the peripheral vascular bed caused primarily by a dilatation of arterioles. The elevation of systolic and diastolic blood pressures, the decrease in pulse pressure, and the slowing of circulation which occurred after thiamine was given, were interpreted as indicating that arteriolar tone increased. This produced a decrease in the volume of the peripheral vascular bed. Consequently, the amount of blood returning to the heart per minute was lowered and the amount of work required of the myocardium was reduced. The authors also suggest that correction of the thiamine lack caused improvement of myocardial function by direct action of the vitamin on the heart. This would indicate that a decrease in muscle tone of blood vessels and of the myocardium in beriberi heart is responsible for the cardiac failure.

Any doubt that deficiency of thiamine is specifically responsible for these circulatory and cardiac changes should be dispelled by the fact that similar abnormalities have been produced in pigeons, rats, and dogs who were made chronically deficient in thiamine. The most recent study is that of Swank and Bessey (*Arch. Int. Med.* **70,** *763 (1942)*). These workers fed pigeons a diet sufficient to prevent significant weight loss but with only 60 to 80 per cent of the normal thiamine requirement. With few exceptions, tachycardia appeared in the chronically deficient pigeons shortly before abnormalities in the electrocardiogram were observed. The most frequent electrocardiographic changes were: (1) an inversion of the T waves in leads II and III, and (2) small (1 to 2 mm.) upward deflections of the Q R S complexes in the same leads. Abnormal electrical potentials were not produced unless the cocarboxylase content fell below 2 micrograms per gram of myocardial tissue. Necrosis of myocardial fibers occurred as a late manifestation in the thiamine-deficient pigeons. The tachycardia and electrocardiographic abnormalities were corrected promptly when additional amounts of thiamine were given. Hydropericardium or other evidences of cardiac failure occasionally were present.

Vasodilatation could commonly be demonstrated.

In discussing the mechanism of the cardiac failure, Swank and Bessey suggest that the tachycardia is due to vasodilatation caused by the local accumulation of intermediate products of carbohydrate metabolism. The vasodilatation also facilitates the transudation of fluid from blood vessels to form hydropericardium, pulmonary edema, and edema of dependent parts of the body. The electrocardiographic changes and the necrosis of myocardial fibers indicate that thiamine deficiency impairs the function of the heart. Myocardial failure, in turn, increases the tendency to increased formation of extravascular fluid. Both clinical and animal investigators, therefore, agree that cardiac failure in chronic thiamine deficiency depends on two factors: impairment of myocardial function, and marked vasodilatation. That cardiac failure may occur as a manifestation of thiamine deficiency seems established.

VITAMIN A NOT EFFECTIVE IN HYPERTENSION

Recently (*Nutrition Reviews* **1,** *21* (*1942*)) reference was made to the experiments of Wakerlin, Moss, and Smith which demonstrated that large daily doses of vitamin A, given parenterally in sesame oil, caused significant lowering of the blood pressure in dogs made hypertensive by the Goldblatt technic. Wakerlin and associates have now extended their observations to show that a highly purified vitamin A concentrate given in daily doses of 400,000 I.U. was without effect in lowering the blood pressure of a "Goldblatt dog" (*Proc. Central Soc. Clin. Res.* **15,** *30* (*1942*)). The reported therapeutic value of vitamin A preparations, therefore, is probably not due to vitamin A itself. Since dogs in which hypertension is induced have neither clinical nor laboratory evidences of vitamin A deficiency, it is not surprising that vitamin A is without effect. The mechanism of the reported therapeutic effect of vitamin A concentrate in experimental renal hypertension in the dog is obscure. Since large doses of vitamin A preparations have been shown to increase the urea, inulin, and diodrast clearances of normal dogs, Wakerlin suggests that the vitamin A concentrate which he used may have altered the pathophysiologic pressor mechanism produced by renal artery constriction.

Wakerlin and associates were stimulated to undertake their study by clinical reports which claimed favorable results in the treatment of essential hypertension in man. However, Taylor, Corcoran, and Page (*Proc. Central Soc. Clin. Res.* **15,** *73* (*1942*)) gave 200,000 I.U. of vitamin A daily to 10 patients with essential hypertension without obtaining significant therapeutic results. Studies of renal function made on 6 of these subjects showed that 5 failed to develop an increase in renal blood flow. The latter workers were, therefore, not able to detect any therapeutic value for vitamin A in the treatment of essential hypertension in man. However, in the light of Wakerlin's new contribution, it should be pointed out that Taylor and associates used a different vitamin A preparation from that employed by Wakerlin and gave about one-tenth the dose on a weight basis. It would be interesting to have these observations repeated with the same concentrate originally used by Wakerlin, with comparable doses, and should any lowering of the blood pressure be observed to attempt a separation of the hypotensive material from the vitamin A preparation.

VITAMIN C METABOLISM IN ADULTS

One practical question concerning studies on vitamin C metabolism is that of the amount of the vitamin required. In general, the criteria which have been suggested for judging the vitamin C needs of adults are similar to those applied to children. Whether maximal values for urinary response to a "saturation" dose, and/or blood ascorbic acid level represent optimal values is still to be decided. There have been several studies in the literature during the past few years, however, which contribute to our knowledge of the response of individuals to various conditions of ascorbic acid intake. The nature of the problem limits the number of individuals which can be studied in any one laboratory at one time. Moreover, the tentative state of our present metabolic criteria accounts for the exploratory nature of many of the studies reported and for the differences in experimental plan and interpretation which are at present encountered. Three studies reported within the last year and reviewed here each illustrate one or more of these points. The most comprehensive of these is a study of 6 individuals on controlled intake levels of 50 to 200 mg. of ascorbic acid over long periods of time, which includes determinations of urinary ascorbic acid excretion and of plasma ascorbic acid. The second study involves 5 individuals in whom the change in "fasting" plasma ascorbic acid during the four hours following ingestion of 50 mg. of vitamin C in crystalline form and in foods was measured. The third study presents the effect on the urinary excretion of 2 individuals on controlled intake levels varying from 40 to 140 mg. of ascorbic acid; on a minimal intake (approximately 5 mg.) for 4 individuals; and of freely chosen diets on 49 individuals. The general inference from these reports is that individuals vary widely in the blood ascorbic acid values and in the urinary excretion of ascorbic acid as related to intake.

Storvick and Hauck (*J. Nutrition* **23,** *111* (*1942*)) add to data already obtained and published by the laboratories of the College of Home Economics at Cornell. Four women and 2 men were first saturated with ascorbic acid and then put on a diet averaging not more than 10 mg. ascorbic acid daily which was supplemented by 200 mg. of crystalline ascorbic acid for all and at levels of 50, 55, 65, 75, 90, 100, 125, and 150 mg. for one or more of the group. Each experimental period was twenty-seven days in length plus a saturation dose of 400 mg. on the twenty-eighth day. This long period on a known intake made possible a thorough study of day to day variations shown by a single individual and also the differences between the other subjects. Most of the adjustment in urinary excretion to a new level of intake took place in the first two or three days, but in general, it was also observed that the daily excretions were by no means constant throughout the whole period and that variations in excretion were greatest on the highest levels of ascorbic acid intake.

The mean daily ascorbic acid excretion on a given intake level differed for the 6 subjects; for example, the 4 women showed excretions of 154 to 164 mg., while the 2 men showed excretions of 130 and 135 mg. on an intake of 200 mg. daily. Since the body weight of the 2 males represented the highest and the next to lowest values for the group, size does not seem to be the factor involved. Urinary pH is also ruled out. The authors are certainly justified in their conclusion that data on more subjects are needed before any decision can be made as to whether the difference noted can be attributed to sex or to some other factor.

In contrast to excretion, plasma ascorbic acid was characteristic for each individual and did not indicate a difference between men and women. The plasma levels on a 200 mg. intake ranged from 1.07 to 1.58 mg. per cent. A study of the 2 subjects (both women) showing the highest and the lowest

plasma levels indicated that their mean urinary excretions were similar. The range of plasma level from day to day for each subject was so wide that in only one case, at higher levels of intake, was the mean value different for a different level of intake. The authors point out that a single value for "fasting" plasma ascorbic acid has little significance as an index of the state of nutrition with respect to vitamin C, although high values are probably indicative of adequate vitamin C in the tissues and low values are usually associated with some degree of tissue depletion. Occasional low values may be expected to occur as a result of errors in sampling (particularly from hemolysis) and in making analyses.

In addition to the twenty-eight day test periods just described, each subject was studied for periods of five to seven days on various levels of intake. Using the lowest excretion of a test dose after a period on 200 mg. intake as the criterion for saturation, the intakes needed to maintain saturation for the 6 subjects were 100, 75, and 125 mg. for 3 of the women and 100 and 150 mg. for the 2 men. If an excretion of 50 per cent of a 400 mg. dose is taken as the criterion for saturation, the needs appeared to be 90, 65, and 90 mg. for the women, and 100 and 150 mg. for the men when the twenty-eight day periods were used. After the two week periods somewhat lower values were found. A marked urinary response to the 400 mg. test dose was observed in all subjects at all intake levels tested, which indicates that none of these levels was low enough to result in severe depletion. For these subjects, there was a definite correlation between the daily urinary ascorbic acid excretion and the concentration of ascorbic acid in the plasma on intakes of 75 mg. and less, but no consistently significant correlation between these two variables on higher levels of intake.

Todhunter, Robbins, and McIntosh (*J. Nutrition* **23,** *309 (1942)*) undertook to determine how rapidly and to what extent ascorbic acid ingested with breakfast would cause a rise in blood plasma ascorbic acid above the "fasting" level. They also studied the effect of ascorbic acid when contained in certain foods as compared to the same amount fed in crystalline form. Five young women were studied. It was found that there was no significant difference between the plasma ascorbic acid in capillary blood taken from the ear and from the finger tip of the same subject. When 50 mg. of ascorbic acid were taken in crystalline form, the blood plasma level showed a slight increase in a half-hour, a definite increase in one hour, and a maximum in one and one-half hours, returning to the "fasting" level in three to three and one-half hours. The same subjects showed the same general picture of absorption rate on each of three different mornings. Orange juice and whole orange, fed at the 50 mg. level, produced results similar to the crystalline ascorbic acid. Strawberries and cauliflower showed a slower rate with a maximum delay of one-half to one hour. The cellular structure of these materials probably accounts for slower digestion and delayed absorption. In contrast to the reports of Storvick and Hauck, these authors report that the "fasting" plasma level tends to remain constant from day to day on approximately the same diet, but fewer determinations were done on a given individual.

The curve for increase of plasma ascorbic acid was not influenced by fat, or by ferrous or ferric salt taken at the same time as the ascorbic acid. When the intake was increased to 400 mg., there was a greater increase in plasma concentration and a longer time elapsed before return to fasting level. When the "fasting" level was below 0.5 mg. per 100 ml., a 50 mg. intake caused no increase in plasma level.

Levcowich and Batchelder (*J. Nutrition* **23,** *399 (1942)*) give additional results on survey studies previously reported and add two studies on urinary excretion of women at different levels of intake which can be compared with those of Storvick and Hauck. The results indicate a correlation between

the urinary ascorbic acid excretion and the calculated vitamin C value of the diet for the preceding seven days. The calculated vitamin C values are apparently high, however, as judged by results when known amounts of ascorbic acid were fed. Studies on 8 young women on a 55 mg. intake indicated an average urinary excretion corresponding to a calculated intake of more than twice that amount. This discrepancy is taken as an indication of the danger of overestimating intakes when calculating diets, and supports the conclusion of Bessey and White that foods other than citrus fruits and tomatoes should not be considered in estimating the vitamin C intake from a dietary history.

Studies on two of the subjects included determinations of urinary excretion after six day periods on fixed levels of ascorbic acid intake, the response to a 400 mg. test dose after each six day period, and capillary fragility. A marked difference was noted in the rate at which the 2 subjects became saturated after subsisting at a test level of vitamin C intake. Capillary resistance was not significantly affected by variation in known ascorbic acid intake. After an extended period on a diet practically devoid of foods containing vitamin C, supplemented by crystalline ascorbic acid, the petechiae found during the capillary resistance test increased in size but not in number.

The urinary ascorbic acid excretions at different levels of intake showed a tendency to rise with higher intakes, but neither these figures nor the percentage excretion of a 400 mg. dose following each period on the test level showed sufficiently consistent and regular increments to justify a conclusion that the higher levels were of specific advantage. There was no subjective or objective evidence of ill effects either at the highest (140 mg.) or at the lowest (40 mg.) levels of ascorbic acid fed. It is concluded that for these 2 moderately active young women a minimal requirement of 50 mg. and a dietary standard (or allowance) of 75 mg. daily is satisfactory.

These three studies are typical of similar reports that have been made on the vitamin C requirement. These studies, as well as the many similar ones, seem to put in the background the important question of what blood level and/or tissue level of ascorbic acid for what length of time is necessary to produce symptoms or signs of ascorbic acid deficiency. The important problem is not how much vitamin C is necessary to keep a certain plasma level or to give a certain urinary excretion but how much is required to maintain good health under a variety of nutritional conditions. With the exception of low plasma levels of vitamin C there is thus far no evidence connecting specific plasma levels of vitamin C with specific functions related to vitamin C or to the general problem of good health.

CALORIC INTAKE AND TUMOR GROWTH

It has long been suspected that the growth and development of tumors might be either retarded or accelerated by changes in diet. All tumors, of course, differ from normal tissues in specific biologic ways, and they tend to resemble each other in that they exhibit "purposeless" growth; yet at the same time all tumors retain many of the general characteristics of the normal tissues from which they have been derived. Since the growth of normal tissues, at least in the young animal, is profoundly sensitive to dietary variation, some sensitivity to diet might also be expected among abnormal tissue.

It is possible to construct diets on which tumors virtually cease to grow. Unfortunately, such drastic deficiencies are involved, as for example the complete omission of proteins or of the vitamin B-complex, that

the host animal is harmed more seriously than the tumor. The practical problem is one of finding dietary combinations that are relatively more deleterious to the tumor than to the host.

One of the simplest ways of achieving this result with experimental tumors appears to be by restricting the caloric intake of the host animal. Many types of inoculated tumors grow more slowly when the intake of calories is reduced by one-third. Some types then fail to grow at all. Tannenbaum (*Cancer Research* **2,** *460* (*1942*)) has observed that not only the growth, but also the production of several tumor types can similarly be minimized by caloric restriction: spontaneous tumors of the lungs or mammary gland, carcinomas due to the local application of benzpyrene, and sarcomas caused by subcutaneous injection of the same hydrocarbon. Several purebred strains of mice were used for each type of tumor. The control full-fed mice grew to weights ranging from 28 to 40 g. The restricted mice were given 50 to 66 per cent of the same diet so that their weights were maintained at 18 to 20 g. The underfed mice were active and sleek, they appeared healthy throughout the experiment, and they lived significantly longer than the controls. The control animals developed high percentages of tumors, while only low percentages of tumors appeared in the restricted groups.

Visscher, Ball, Barnes, and Sivertson (*Surgery* **11,** *48* (*1942*)) used a different method of restricting calories. Their diets were compounded so that the daily intake of salts, proteins, and vitamins was the same in the full-fed and in the restricted groups, while the percentages of fat and carbohydrate were reduced to produce a 33 per cent restriction in total caloric intake. A high percentage of spontaneous mammary tumors appeared in the full-fed mice while no tumors developed in the restricted controls.

Since the two methods of restriction yielded similar results, it appears that the intake of calories *per se* is more important for the development of these particular tumor types than the ratio of total calories to proteins, salts, or vitamins. No satisfactory picture has as yet been offered of the means by which a reduction in calories hinders the formation of tumors, nor has the phenomenon been correlated with the idea that the tumor-cell contains "damaged" enzyme systems as compared to the normal. Tannenbaum, however, has emphasized that the effects of caloric restriction must be general.

It would certainly be premature to suggest changes in human diets based on the present results with experimental tumors. Nevertheless, it is curious that an extensive survey of the dietary habits of cancer patients (Hoffman, *Diet and Cancer*, Baltimore, (1937)) indicated that cancer patients had been eating more of fats, proteins, carbohydrates, and minerals than noncancer patients; also that cancer patients had been eating more of each of several hundred different items common in the American diet. The results probably merit more serious attention than the remark of one investigator, that "eating is carcinogenic." Certainly in any study of the relation between diet and tumor development, it must be established that the caloric factor has been controlled before variations in tumor incidence can be attributed to specific components of the diet.

VITAMIN A CONCENTRATES AFFECT MILK

As early as 1913, Casimir Funk suggested that there was probably a definite relationship between the amount of vitamin secreted in milk and that ingested in feed. Quantitative experimental evidence regarding vitamin A relationships between feed and milk

was lacking until the work of Kennedy and Dutcher was published (*J. Biol. Chem.* **50,** *339 (1922)*). Since that time many investigations have been conducted to show that the vitamin A potency of butterfat is related directly to the carotene content of the ration and that vitamin A, *per se*, plays a negligible role in the normal dairy ration so far as the vitamin A potency of cow's milk is concerned.

Numerous attempts have been made to increase the vitamin A content of milk by feeding methods. Baumann and Steenbock (*J. Biol. Chem.* **101,** *547 (1933)*) were among the first to show that summer butter was 400 per cent richer in carotene than winter butter, while the increase in vitamin A amounted to not more than 200 per cent. In 1926 Golding, Soames, and Zilva (*Biochem. J.* **20,** *1306 (1926)*), attempted to increase the vitamin A content of milk by feeding cod liver oil to dairy cows. Their findings, which were later confirmed by other laboratories, led to the conclusion that this could not be considered a practical method because of the apparent toxicity of cod liver oil. Detrimental effects on appetite, milk production, and milk fat levels were ascribed to the glyceride portion of cod liver oil.

In 1941, Deuel and co-workers (*J. Biol. Chem.* **139,** *479 (1941)*) described experiments in which shark liver oil of high vitamin A potency was fed to dairy cows without ill effects so far as milk production and butterfat levels were concerned. Bioassay methods indicated that, in the nineteenth week of the experiment, control butterfats averaged 21 I.U. per gram as compared with 155 I.U. per gram of butterfat from a cow that had received 1,400,000 I.U. of vitamin A in the form of shark liver oil. These workers also stressed the favorable effect of shark liver oil on milk production and the content of butterfat.

Recent (and more comprehensive) studies by Deuel and co-workers (*J. Nutrition* **22,** *303 (1941); Ibid.* **23,** *567 (1942)*) confirm the early work with reference to the increase of vitamin A in milk and butterfat by supplementing the dairy ration with shark liver oil of high potency. When shark liver oil was fed in doses too small to cause an increase in the level of vitamin A, marked decreases of milk carotene were noted. Daily supplements of less than 700,000 I.U. were ineffective in causing increases of vitamin A in milk. Decreases in milk carotene seemed to be caused by vitamin A itself. The maximum level of vitamin A recorded in these studies was 331 I.U. per gram of butterfat and the efficiency in secretion of ingested vitamin A was about 3 per cent.

The most recent paper relative to the feeding of shark liver oil is that of Jensen and associates (*J. Dairy Sci.* **25,** *931 (1942)*). These writers disagree with Deuel and co-workers only in regard to the effect of shark liver oil on milk production and the per cent of butterfat. A total of 28 cows, representing 4 dairy breeds, were used in the study. Two shark liver oils with respective potencies of 26,650 and 15,400 I.U. per gram were used as the source of vitamin A. Daily supplements of vitamin A ranged from 770,000 to 1,332,500 I.U.

Estimations of vitamin A, ascorbic acid, and carotene were made on blood serum and on vitamin A and carotene in milk. Distinct rises in blood plasma vitamin A were brought about when shark liver oil was fed, but the higher supplements had no advantage over the lower supplements in this regard. This is interpreted to mean that the cows were adequately fortified with vitamin A from the beginning of the experiment, since plasma vitamin A was 0.19 micrograms per ml. or higher. Plasma from cows receiving moderate or high levels of vitamin A ranged from 0.20 to 0.37 micrograms per ml. of vitamin A. Carotene content of the milk diminished as vitamin A dosage increased. No explanation of this phenomenon could be found. Plasma ascorbic acid was not changed by vitamin A

supplementation, the average of all animals being close to 0.40 mg. per cent.

The findings of these Wisconsin workers confirm the findings of Deuel and co-workers relative to the effect of high intakes of vitamin A on the amount of this vitamin found in the milk and butterfat. They also agree that carotene is lowered as vitamin A dosage increases, and that little increase in vitamin A is obtained by shark liver oil feeding. They found that only 2.2 per cent of the vitamin A actually finds its way to the milk. This agrees closely with Deuel's figure of 3 per cent.

Jensen *et al.* have been unable to find that shark liver oil causes an increase in milk production or in per cent of butterfat in the milk. In fact, they found that daily doses of as much as 90 ml. of shark liver oil seemed to hasten the normal rate of decline of milk production with the advance of lactation.

MINERAL METABOLISM IN MAN

The importance of mineral metabolism in animal life has long been appreciated. In laboratory and farm animals the mineral requirements have been carefully studied and much is understood of their role in animal physiology. Much less is known definitely concerning the mineral metabolism of man, but valuable information has recently been obtained from several laboratories.

Johnston and Roberts (*J. Nutrition* **23,** *181 (1942)*) studied the iron requirements of children of school age who were kept in institutions and whose diets were uniform. Twenty-one children between the ages of 8 and 11 years were divided into three groups, and were given three graded levels of iron. The hemoglobin content of the blood was used as the criterion of adequacy. Cell counts were likewise made. By analyzing the diet for iron and checking the blood for hemoglobin these authors were able to determine over a period of seven months the minimum iron requirement that would maintain hemoglobin concentrations within the normal range. Children who showed good hemoglobin levels had been maintained on daily intakes of 10 to 15 mg. of iron or 0.35 mg. of iron per kilogram of body weight. Data were not available on lower intakes. Such a level of iron ingestion maintained hemoglobin at the normal level of 12 to 14 g. per 100 ml. of blood.

The iron requirement established by Johnston and Roberts for school children of 8 to 11 years of age is remarkably close to the requirements determined for young women between the ages of 16 and 27 years by Leverton and Marsh (*J. Nutrition* **23,** *229 (1942)*). These authors made observations for a week on the iron metabolism of 69 young women. They found that a daily ingestion of 10.44 mg. of iron provided an average daily storage of 1.37 mg. which was ample to replace normal menstrual losses. The type of diet was found to influence the utilization of the iron. Seven subjects on a generous nutritive plane maintained a positive balance on a daily intake of 7.21 mg. of iron while 5 other subjects on a similar iron intake, but suboptimal diets, were in a negative iron balance. These studies indicate that the iron absorption and metabolism were favorably influenced by other factors in the diet.

The type of diet has also been shown by McKay and co-workers to influence calcium retention (*J. Nutrition* **24,** *367 (1942)*). In a study of 124 college women between the ages of 17 and 24 years these authors found that the type of diet was one of the important factors influencing calcium retention. Supplements of 1, 2, and 3 cups of milk brought about greater calcium retention than when self-chosen diets were used. The increase in retention was not due entirely to

the intake of more calcium because the milk improved the diet in other factors which improved calcium retention. Thus the retention of calcium was related not only to calcium intake but also to the general adequacy of the diet. The mean daily intakes necessary to maintain equilibrium were found to be 0.8 g. of calcium, 1 g. of phosphorus, and 9 g. of nitrogen. The authors draw attention to the similarity of their results and the recommendations of the Committee on Foods and Nutrition. Their point that for some purposes it is more desirable to have large numbers involved in this type of study rather than an intensive study of a single individual appears to be well founded. As far as calcium, phosphorus, and nitrogen requirements are concerned, the old rule is still good, namely, that a pint of milk per adult per day, and at least a quart per child per day, is sound nutritional practice.

That calcium retention is not directly related to the protein of the diet has been suggested by Hawks, Bray, Wilde, and Dye (*J. Nutrition* **24,** *283 (1942)*) who studied the influence of protein upon calcium and phosphorus metabolism. They fed 5 children first 3 g. then 4 g. of protein per kilogram of body weight. Two children received eggs, meat, and milk while the others were given egg white and gelatin. The higher protein diet had no effect upon calcium retention and apparently caused a decrease in phosphorus absorption. Growth was better on 4 g. of protein than on the 3 g. level.

These studies, like those reported on potassium, sodium, and chlorine balances by Hawks and co-workers (*J. Nutrition* **24,** *437 (1942)*), do not cover a sufficient number of cases to make the work conclusive. Detailed analytical records were obtained on a few children but it is uncertain whether they indicate the actual mineral requirements of children. Retention of potassium may be largely independent of dietary protein and may on the other hand be related to other necessary nutrients. Until more of the variables can be adequately isolated and controlled and clearcut data obtained, such studies can be used only as a rough guide in setting up man's dietary requirements.

THE ETIOLOGY OF "ALCOHOLIC" POLYNEUROPATHY

The classic descriptions of "alcoholic" polyneuropathy and of the polyneuropathy of beriberi are so much alike as to be interchangeable. Nevertheless, and despite the fact that Vedder showed as early as 1913 that beriberi was caused by the lack of vitamin B_1, it was not until 1925 that Gigon and Odermatt (*Z. ges. exp. Med.* **47,** *294 (1925)*) first suggested that, in "alcoholic" polyneuropathy, "the vitamin content of the organism is perhaps involved." In 1928 Shattuck suggested that some cases of polyneuropathy which developed in the course of various debilitating diseases might be properly regarded as true beriberi. This concept was echoed by Minot in 1929. In 1933 Wechsler definitely concluded from the study of clinical cases that avitaminosis played a definite, and possibly the decisive, role in the production of polyneuropathy. Following this there appeared in the literature a series of articles by a number of authors tending to implicate the antineuritic vitamin B_1 as the substance, the lack of which is responsible for the development of the classic polyneuropathy of the chronic alcoholic. There is an excellent review of the subject by Jolliffe (*Quart. J. Studies on Alcohol* **1,** *517 (1940)*).

When crystalline thiamine became available for clinical investigation, Goodhart and Jolliffe (*J. Am. Med. Assn.* **110,** *414 (1938)*) tested the effectiveness of this substance in the treatment of mild cases of "alcoholic" polyneuropathy. They found that when 10 mg. of thiamine were administered daily to subjects receiving high vitamin diets, both

the rate and degree of recovery were significantly increased over those of a control group which received only the high vitamin diet. Crystalline thiamine has been used extensively since 1938 for the treatment of alcoholic polyneuropathy with varying degrees of success. Among the reasons for therapeutic failures are included inadequate vitamin dosage, tardy administration of therapy in acute cases and, in chronic cases, the institution of therapy only after slowly reversible nerve degeneration changes had occurred. It is probable also that not all the polyneuropathies occurring in the alcohol addict are due primarily to nutritional deficiencies. Acute infectious polyneuritides may occur. Again, alcohol addicts rarely if ever suffer from a single vitamin deficiency. Combinations of deficiencies of vitamins A, C, and various members of the B-group are known to be the rule. Several of these, other than thiamine, are known to cause pathology of the nervous system. It is possible that in some instances a lack of one or more of these substances may play an adjuvant or, in certain cases, even the main role in the production of the polyneuropathy.

What has been sorely needed to confirm the close association of thiamine deficiency with "alcoholic" polyneuropathy has been a simple test, or tests, to prove that in the active stages of this disease there exists, not only a deficiency of thiamine, but a deficiency severe enough to cause a metabolic disturbance.

In 1939, Banga, Ochoa, and Peters (*Biochem. J.* **33,** *1980* (*1939*)) proved the diphosphoric ester of thiamine (cocarboxylase) to be essential for the catabolism of pyruvic acid. Lee (*Biochem. J.* **33,** *774* (*1939*)) and Platt and Lee (*Quart. J. Med.* **5,** *355* (*1936*)) demonstrated increased amounts of pyruvic acid in the blood and tissues of vitamin B_1 deficient animals and human beings suffering from beriberi. Wortis, Bueding, and Jolliffe (*New Engl. J. Med.* **226,** *376* (*1942*)) have shown recently that there exists a similar increase in the pyruvic acid content of the blood of alcoholic addicts with acute peripheral neuropathy.

Previous determinations on 60 normal subjects by Bueding and Wortis (*J. Biol. Chem.* **133,** *585* (*1940*)) showed the normal range in blood pyruvic acid content to vary from 0.77 to 1.16 mg. per 100 ml., averaging 0.98 mg. All samples were obtained on fasting subjects at rest in bed. Wortis and associates did blood pyruvic acid determinations on 48 alcoholic patients with acute peripheral neuropathy, 25 with chronic peripheral neuropathy, and 22 without any evidence of nutritional deficiency. Spinal fluid estimations were also made in a number of instances.

Forty-five of the 48 subjects with acute peripheral neuropathy had blood contents of pyruvic acid above 1.30 mg. per cent (1.16 being the highest observed normal value). The other 3 subjects had blood values between 1.0 and 1.30 mg. per cent. All the blood values for the 25 subjects with chronic peripheral neuropathy and the 22 showing no evidence of nutritional deficiency were below 1.30 mg. per cent. The spinal fluid values were entirely in line with the blood levels in all cases where they were determined.

"In 14 cases of acute peripheral neuropathy, pyruvic acid curves following glucose ingestion were abnormally elevated and prolonged. The maximum rise in blood pyruvate was not only greater than that seen in normal subjects, but the elevation above the fasting level was maintained for at least four hours. Furthermore, the maximum rise did not occur at the end of the first hour, as in normal persons, but the pyruvate continued to rise in every case, and maximal figures occurred at the end of the second, third, or fourth hour. Particular mention must be made of one case of acute peripheral neuropathy with a normal fasting blood pyruvate, and a markedly abnormal pyruvate curve following glucose ingestion." This case is one of the three previously mentioned as having normal fasting blood pyruvate

values. The other 2 subjects with normal fasting blood values were the only two of the 48 patients with acute peripheral neuropathy who failed to improve following adequate thiamine therapy. It may be that these 2 subjects represented examples of infectious neuritis or, more likely, that they were incorrectly diagnosed acute, whereas the presence of severe anatomic lesions should have merited their classification in the chronic group.

The chronic cases included subjects who had previously received adequate vitamin therapy without return to normal functioning of the peripheral nerves and subjects who had been on hospital diets for some time. It is understandable, then, why they did not demonstrate any abnormality in pyruvate metabolism at the time of the test. The active stage of the disease had departed, leaving a residuum in the form of anatomic lesions. It is interesting that the alcoholics who showed no manifestations of nutritional deficiency also showed no significant elevations in their fasting blood pyruvate levels. This would suggest that, if elevated fasting blood pyruvate levels do indicate thiamine deficiency, their determination would be of no value as a diagnostic aid for any stage of thiamine deficiency less than the most severe stages such as polyneuropathy, Wernicke's encephalopathy, and beriberi.

Wortis and associates conclude that "the relation of hyperpyruvemia to cases of acute peripheral neuropathy suggests that this disease is associated with a deficiency of thiamine." Goodhart (*J. Clin. Invest.* **20,** *625 (1941)*), working in the same hospital and in some instances with the same subjects, has demonstrated variations in the thiamine content of the blood in alcoholics which strengthen this conclusion of Wortis, Bueding, and Jolliffe.

Using the yeast fermentation method of Atkin, Schultz, and Frey (*J. Biol. Chem.* **129,** *471 (1939)*), Goodhart found the average fasting blood content of thiamine for normal subjects (86 determinations on 45 volunteers) to be 5.39 micrograms per cent, with a range from 3.1 to 9.2 micrograms. Only one of 27 alcoholic patients with no clinical manifestations of nutritional deficiency had a blood level of thiamine below 3.1 micrograms per cent. This subject "was admitted to the hospital suffering from acute alcoholic intoxication and hypoglycemic shock. He was treated with glucose infusions and the blood thiamine determination was made on the following day, at which time he was asymptomatic."

Twelve of 17 subjects with acute "alcoholic" neuropathy had blood thiamine values below the lowest observed normal value. Four of the remaining 5 subjects had values that were definitely below normal. In contrast, 10 of the 16 subjects with chronic "alcoholic" neuropathy showed blood thiamine values within normal limits. In a total of 106 subjects, including 28 non-alcoholic patients with a variety of medical and psychiatric disorders, blood thiamine values below 3.1 micrograms per cent were found in 22 instances. In only 4 cases was such a value found in the absence of neuropathy. These included one subject with severe general and cerebral arteriosclerosis, one with advanced miliary tuberculosis, one with lymphoepithelioma, and the alcoholic mentioned in the previous paragraph.

It would appear that determinations of the total blood thiamine content can be of no greater aid in the diagnosis of early and mild thiamine deficiency states than the fasting blood pyruvate. Although blood pyruvate determinations lack the specificity of blood thiamine determinations, the methods for the estimation of pyruvate are more accurate, more foolproof, and more amenable to adaptation to clinical laboratory facilities. The blood pyruvate is apt to be elevated, in the absence of thiamine deficiency, in cases complicated by marked elevations in temperature (Wortis *et al.* found hyperpyruvemia in 22 of 35 such cases). It is likely to be elevated in tests performed without strict observance of basal

conditions. These situations, however, are all capable of recognition or control.

The results obtained by Wortis, Bueding, and Jolliffe, and by Goodhart, using laboratory procedures, considerably strengthen the case constructed by clinical investigators, from case histories and therapeutic trials, for a prime cause and effect relationship between thiamine deficiency and "alcoholic" polyneuropathy.

FEEDING INDUSTRIAL WORKERS

With the development of mechanized warfare, great armies of industrial workers have become as important to the conduct of war as the armed services. The size of the armies which a nation can now afford to mobilize for combat duty depends to a great extent upon the productive capacities of the nation's war industries (including agriculture and transportation facilities). It can no longer be determined through a mere enumeration of the male population of military age. The rapid and great expansion of our war industries and of our Army and Navy has made it imperative for our government to explore all sources of available man- and womanpower. When our industries are more efficiently managed, and when the individual worker becomes more productive, more men can be released for the armed forces. The problem of manpower, then, has two major aspects; one of mobilization, and another of conservation.

Every individual in an essential industry must be kept, in so far as possible, at the peak of working efficiency. The human being is a complex organism, reacting to and being influenced by a large variety of environmental factors, so that the administration of his activities is not a simple affair. However, it is fundamental that he be maintained in good health if his energy output is to remain at its peak for any period of time. The maintenance of health involves adequate housing, recreation, sleep, sanitation, disease and accident control measures, and nutrition. If it could be said that any one of these measures of health control demands greater consideration than another at the present time, that one would be nutrition, if for no other reason than that the nutrition of industrial workers has received a minimum of attention from responsible quarters.

Sawyer (*Med. Clin. of N. A.*, **26**, *1067 (1942)*) in an article which is largely an abstract of the first report of the Committee on Nutrition in Industry of the Food and Nutrition Board of the National Research Council (N.R.C. Reprint and Circular Series No. 110, April, 1942) states that many dietary deficiencies exist among industrial workers. Dr. Sawyer is medical director of the Eastman Kodak Company, Rochester, New York. He recommends that industrial plants have their own scientifically planned programs on nutrition for their employees. Such programs should place dietitians or nutritionists, who would be available at regular hours for individual nutrition advice, in complete charge of the service of food within the plant. They should ensure the "provision of proper and adequate menus" for plant cafeterias, food wagons, and canteens. "With a trained person heading the industrial cafeteria, food will be more wisely purchased and the charge to the employee less. Standardized recipes will be used in food preparation and menus planned that will be nourishing and adequate and at the lowest possible cost. Offering the employees a complete plate lunch is the best method of selling good nutrition. Cafeterias that offer a hot plate lunch of this type at 25 or 30 cents usually do an excellent business."

Dr. Sawyer thinks that, although it is true that with a good diet vitamin supplementation should not be necessary, conditions in industry are such that it is unlikely

that the majority of workers can be assured good diets. For this reason, the medical department of the Eastman Kodak Company advocates "vitamin therapy to all employees who are subject to upper respiratory infections, under- and overweight, and those working overtime under undue physical and nervous strain." This view is at variance with the attitude of the Committee on Nutrition in Industry of the National Research Council and with that of the Nutrition Division of the Office of Defense Health and Welfare Services only in so far as it appears to be more inclined toward the use of vitamin supplements for industrial workers. There is no evidence that any of the vitamins in the amount in which they are generally given for prophylactic purposes are harmful; they are harmless, if somewhat expensive, preparations. However, there are many essential food factors other than those generally included in polyvitamin preparations. Two or 3 mg. of thiamine do not make up for a lack of pyridoxine, iron, protein or any other factor essential to the nutrition of man. The basis for good nutrition must be natural foodstuffs. This does not mean than one cannot use vitamin concentrates or synthetic vitamins when it is impossible to get everything from one's diet. There are certain methods of cooking, preparing, and storing foods which are essential for the preservation of their vitamin content. In the tropics, and in some sections of this country, there is little or no refrigeration, and cooking facilities are not adequate. In other instances there may be no practical way to prepare and serve food on a mass scale so that the vitamin content is retained. However, before vitamin concentrates are used, every effort should be made to supply adequate meals of natural foodstuffs.

There are many situations in industry where it is not feasible to provide the workers with a nutritious hot meal at the plant. There is nothing intrinsically meritorious about a hot meal; it is possible for a cold meal to be much more nutritious than a hot one. The "dinner pail" and cold lunch should be improved, rather than condemned. The hot meal in some instances is certainly to be condemned, particularly when it remains on a steam table for an hour or more after preparation. A great deal of loss in vitamin content may occur under such conditions.

In addition to the problem of the regular meal, there is the problem of between-meal feedings. The Committee on Nutrition in Industry of the National Research Council recommends five meals a day for the industrial worker under some circumstances, that is, three small meals in the plant rather than one large meal. In every instance where this has been tried, production has been increased. The Committee has recommended that plants space their meal periods not more than four and a half hours apart under any circumstances.

Between-meal refreshments should consist of something more than candy and soft drinks. The idea that sugar is a more important source of ready energy for industrial workers than the starches is fallacious. Comparative studies on the absorption of simple sugars and the absorption of carbohydrate in the form of starches, in bread, have shown that differences in the rates of absorption are so slight that they normally are not of any physiologic importance. Between-meal feedings should consist of foods which are more nutritious than the highly refined sugars.

There is another important problem in relation to nutrition of industrial workers and that is the problem presented by shift work. The cafeterias of many plants are open only for the day shift. This is particularly true of concessions that are run for a profit, as the "swing" and the night shifts have not proved profitable during peacetime. Generally the nutritional status of the "swing shift" worker is worse than that of the day shift worker. He frequently finds it difficult to get good meals before reporting

for work and after leaving the plant in the middle of the night. There are several ways in which the plant might attack this problem. Arrangements could be made with a neighborhood cafeteria to stay open, guaranteeing to the management a certain amount of business and getting the men to cooperate, or the plant may arrange to have its own cafeteria open for these men so that they can get a good meal when they leave work.

Another problem in relation to shifts is the rate of change. Some plants change their shifts every two to three weeks. Such rapid changes have generally proved to be inefficient. Highest production is most often maintained when the workers are kept on one shift long enough to become acclimated to the hours and work. The U. S. Public Health Service has recommended a period of at least two to three months.

Unfortunately, not much is known about the particular food needs of workers in industries which expose them to toxic substances or conditions of unusual physiologic stress. We do know that under conditions of extreme heat, where there is considerable perspiration, there is increased salt loss. There may also be loss of water soluble vitamins. Sugar has been advocated for the prevention and treatment of heat exhaustion, heat cramps, and heat stroke. There is no evidence that sugar is of value in combating any of these conditions in industrial workers.

Many industrial physicians are not interested in the management of the plant cafeteria or canteen, but concern themselves principally with sanitation, accidents, toxicities, and food poisoning. Their function should be much broader than that and they should take an active interest in the worker's nutrition problems. Actually the campaign to assure an adequate food intake by industrial workers has been hampered by the lack of interest of physicians, particularly industrial physicians, in the potentialities of good nutrition. The publication of Dr. Sawyer's interesting article in a symposium on industrial medicine may serve to draw the attention of industrial physicians and gain their active cooperation in the problem of nutrition in industry.

MECHANISM OF CAROTENE OXIDATION

Almost from the time that it became known that carotene functions as provitamin A, nutrition workers have been interested in studying the factors affecting carotene stability. Carotene has long been known to be particularly susceptible to oxidative destruction. During storage and processing many plant materials undergo rather rapid bleaching, with accompanying losses of carotenoid pigments. These losses have been measured by biologic, chemical, and physical methods. Numerous researches on crops, dried by natural and artificial methods, have shown that enzymatic action seems to play an important role in carotene destruction.

In 1928 Bohn and Haas discovered an enzyme in legumes, the properties of which Sumner and Dounce described in 1939. These workers showed that this enzyme, which they called "carotene oxidase," would not oxidize carotene or bixin unless fats were present. Unsaturated fats, such as hempseed or soybean oil, were far more effective than olive oil or butter. They expressed the opinion that the bleaching action of the enzyme was probably "an instance of a coupled reaction."

Later work indicated that lipoxidase converted unsaturated fats into peroxides and that carotene destruction occurred simultaneously. Consequently, some workers felt that carotene destruction could be explained by assuming that the oxidation of carotene is brought about by the action of the fat peroxides. In a recent paper Sumner (*J. Biol. Chem.* **146,** *215 (1942)*) offers evi-

dence to prove that the above explanation is incorrect. He goes so far as to state that carotene is not oxidized, directly or indirectly, by peroxides formed from unsaturated fats. To prove his point, Sumner strongly peroxidized linseed oil with aqueous soybean meal extracts. This peroxidized fat was incapable of decolorizing carotene solutions even after several hours

Further experiments led to the conclusion that rapid oxidation of carotene is brought about neither by the direct action of fat peroxides nor by the presence of an enzyme which acts as an oxygen carrier from fat peroxides to carotene. Sumner advances the hypothesis that unsaturated fat must be in the process of oxidation to effect rapid carotene oxidation by this system, perhaps by giving rise to an unstable intermediate oxide.

IRON ABSORPTION IN MAN

Our information about iron absorption has been augmented considerably since Hahn, Whipple, and their associates began using radioactive iron to study its absorption. Since radioactive iron is "tagged," it can be detected and measured with comparative accuracy as it appears in the blood stream and organs of storage. Hahn has demonstrated that normal animals apparently absorb only small quantities of iron while iron-depleted animals retain large amounts of a given dose. In their efforts to explain these results, Hahn and Whipple have assigned to the intestinal mucosa the ability to assimilate iron selectively—to accept or refuse the metal according to body needs.

A few laboratories are applying this technic to the study of iron absorption in human beings. The first complete report of one of these investigations has been made recently by Balfour, Hahn, Bale, Pommerenke, and Whipple (*J. Exp. Med.* **76,** *15 (1942)*). These authors fed varying amounts of radioactive iron as ferric ammonium citrate to normal subjects and to patients with various hematologic disorders. One normal medical student absorbed 1.8 per cent of the amount given. Several patients who had been bleeding from peptic ulcers assimilated 15 to 20 per cent of the radioactive iron. It is rather surprising that in one woman with a hypochromic (iron deficient) anemia only 2 per cent of the material appeared in the peripheral blood. No free acid was present in the gastric juice, however, hence anacidity may have interfered with absorption. This patient subsequently responded satisfactorily, with a hemoglobin rise, to the administration of therapeutic amounts of iron. Subjects with a normocytic anemia apparently produced by an infection retained only a small percentage of the iron given. Patients in whom the iron stores were presumably high (pernicious anemia, hemolytic anemia, hemochromatosis, polycythemia) absorbed only 1.7 per cent or less of a single dose of radioactive iron. One child with leukemia (monocytic) showed only 0.6 per cent in the circulation, and at autopsy four months later only 1.5 per cent was found in the liver, spleen, and heart.

Fourteen pregnant women were studied. Two of these absorbed only "normal" amounts of iron while the remaining twelve retained two to ten times the quantity that would be expected of normal controls. The conclusion is reached, therefore, that the human being, like the dog, absorbs more iron when stores are depleted and rejects it when the storage depots are well supplied. Of special interest is the observation that most pregnant women apparently absorb (and hence are in need of) greater amounts of iron than do comparable control subjects. While the value of these observations is unquestioned, it is rather unfortunate that

only one form of iron was used for administration and that the size of the dose was not standardized in terms of body weight.

One possible objection to the use of the radioactive iron technic as a gauge of iron absorption is that the individual with adequate stores of the metal may absorb the iron but simply retain it in the tissues. When new hemoglobin is formed, both normal and radioactive iron might be used, but the rate of hemoglobin synthesis might not be great enough to demand that all the radioactive form be withdrawn from the stores. If this were true, the quantity of radioactive iron in the circulating blood would not serve as an adequate measure of the amount of iron that had actually been retained. In order to study this possible objection, Balfour and collaborators removed 500 ml. of blood from several of their subjects. In no instance, however, did they succeed in removing appreciable amounts of radioactive iron from the tissues by stimulating massive hemoglobin production in this manner.

Ross and Chapin (*J. Clin. Invest.* **20,** *437* (*1941*)), using ferric iron and a technic similar to that of Balfour, also observed that normal human beings absorbed only small quantities of radioactive iron while patients with hypochromic anemia retained comparatively large amounts. Moore, Roberts, and Minnich (*J. Clin. Invest.* **20,** *436* (*1941*)) agreed that normal human beings given radioactive iron as ferric chloride absorb but little of the material, but when iron was given in the bivalent or ferrous state, much larger quantities appeared in the peripheral blood. This last observation agrees with the widely held clinical impression that human beings absorb ferrous better than ferric iron and suggests that final appraisal should be withheld until studies like that of Balfour's are reported in which both forms of iron are used in the study of absorption.

PARA-AMINOBENZOIC ACID AND SULFONAMIDE DRUGS

A few years ago D. D. Woods demonstrated that para-aminobenzoic acid antagonizes or "blocks" the bacteriostatic effect of sulfanilamide *in vitro* (*Brit. J. Exp. Path.* **21,** *74* (*1940*)). He postulated that since p-aminobenzoic acid and sulfanilamide are structurally similar (both have an amino group in the para position on a benzene ring), the antagonism might depend on a competition between these two substances for an important enzyme site on the bacterial cell. In advancing this theory, Woods assumed that p-aminobenzoic acid, one of the B-complex vitamins, is an essential bacterial metabolite; and that when its position is taken by sulfanilamide in one of the bacterial enzyme systems, growth of the organisms is no longer possible. Experimental proof confirming the first of these two assumptions has been provided by Lampen and Peterson (*J. Am. Chem. Soc.* **63,** *2283* (*1941*)) and by C. R. Park and W. B. Wood, Jr. (*Bull. Johns Hopkins Hosp.* **70,** *19* (*1942*)). The latter workers demonstrated that p-aminobenzoic acid and biotin are required as growth factors by the bacterium *Clostridium acetobutylicum*. Proof for the second assumption will probably have to wait until the involved enzyme systems are chemically separated and studied.

It has recently been demonstrated by W. B. Wood, Jr. (*J. Exp. Med.* **75,** *369* (*1942*)) that the antagonism between p-aminobenzoic acid and the more common sulfonamide drugs is quantitative, that is, as the concentration of sulfonamide compounds increases, more p-aminobenzoic acid is required to nullify the bacteriostatic effect. Over a wide range of concentration, the minimum amount of p-aminobenzoic acid needed to prevent bacteriostasis is such that the ratio of p-aminobenzoic acid to

sulfonamide concentration is constant. Wood used *Bacterium coli* in his experiments since it grows luxuriantly in an inhibitor-free medium containing only asparagine as a source of nitrogen, glucose as a source of carbon, and inorganic salts. The addition of p-aminobenzoic acid to the medium has no effect on the rate of growth of the organisms. Six different sulfonamide drugs were employed in the study: sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfaguanidine, and diaminodiphenylsulfone. The amount of p-aminobenzoic acid required to neutralize the bacteriostatic effect of each varied widely. Sulfathiazole, for example, demanded much greater concentrations of the vitamin than did sulfanilamide. Furthermore, the bacteriostatic potency of each sulfonamide drug was found to be directly proportional to its ability to counteract the antibacteriostatic influence of p-aminobenzoic acid. It is interesting to note that one molecule of p-aminobenzoic acid will antagonize the action of several thousand sulfonamide molecules. Wood suggests that this fact need not invalidate the theory that the sulfonamide drugs, through their chemical similarity to p-aminobenzoic acid, succeed in blocking the enzyme system normally involved in the utilization of the latter substance and so keep bacteria from growing. He postulates that it may indicate only that p-aminobenzoic acid has a far greater affinity for the enzyme than have the sulfonamide drugs; hence a great excess of the drugs is required before the vitamin is blocked from its enzyme system.

Wood and Austrian (*J. Exp. Med.* **75,** *383 (1942)*) also studied the effect of niacinamide, cozymase, and cocarboxylase in blocking the bacteriostatic action of sulfonamide drugs. They pointed out that sulfapyridine was structurally similar to niacinamide and cozymase in that each possessed a pyridine nucleus. Likewise, the thiazole ring is common to thiamine, cocarboxylase and sulfathiazole, while sulfadiazine, like cocarboxylase and thiamine, contains a pyrimidine radical. However, the antisulfanilamide effect of these vitamins (or derivatives) was not specific and exerted its antagonism whether structural similarity existed or not. The experiments of Wood and Austrian indicate that cocarboxylase and cozymase exert their antisulfonamide action by stimulating bacterial growth rather than by antagonizing the drugs directly. This mechanism, therefore, differs sharply from that for p-aminobenzoic acid.

These studies help to explain how sulfanilamide and its derivatives act. They add considerable information to our understanding of bacterial metabolism and of the metabolites essential to bacterial growth. That they may stimulate other important advances is indicated by the fact that sulfanilamide has been shown to possess some of the nutritional value of p-aminobenzoic acid. Martin (*Proc. Soc. Exp. Biol. Med.* **51,** *56 (1942)*) demonstrated that when sulfanilamide replaces p-aminobenzoic acid in a purified diet containing 7 B-complex factors including inositol, it partially prevents the development of a syndrome heretofore associated with a deficiency of p-aminobenzoic acid.

RENAL DAMAGE IN CHOLINE DEFICIENCY

Choline is now recognized as an important dietary factor. In its absence in the experimental rat, excessive lipids are deposited in the liver, involution of the thymus occurs, and there is a marked congestion of the kidney with hemorrhage.

The histopathology of choline deficiency has been studied by Christensen (*Arch. Path.* **34,** *633 (1942)*). Choline deficient young rats were obtained from Griffith (*J. Biol. Chem.* **131,** *567 (1939)*) and used for histologic examination. The gross pathol-

ogy was marked by engorgement of the superficial zone of the kidney with mottling and congestion of the surface. The peripheral zone showed a deep red color. Histologic changes noted were vascular congestion of the cortical capillaries with tubular necrosis followed by many large hyaline casts. If the young animals survived, spontaneous regeneration occurred with recession of the congestion, interstitial fibrosis, and subsequent calcification. There was a slight reduction in the size of the glomeruli.

This study of the histopathology of a choline deficiency is particularly significant because of the striking similarity of the pathology of this disease to the pathologic conditions of the human kidney variously reported as symmetric necrosis, acute ischemic renal necrosis, and preeclamptic toxemia. The etiology of these diseases is not known.

Sheldon and Hertig (*Arch. Path.* **34,** *866 (1942)*) have reported 2 cases of symmetric cortical necrosis of the kidneys following toxic separation of the placenta. The kidneys in these cases presented numerous confluent patchy areas of necrosis confined to the cortex. The histologic observations showed the afferent capillaries to be degenerated particularly as they entered the glomeruli, with the formation of thrombi and hemorrhage. The authors report a retrograde extension of the process in the intralobular and interlobar arteries with resulting ischemic necrosis. Similar vascular lesions resulting in necrosis were found in the anterior lobe of the pituitary, the pituitary stalk, and the region of the tuber cinereum at the floor of the third ventricle. They also appeared in the cecum and the adrenal. Thus the kidney pathology that occurred in these 2 cases is closely parallel to that which appears experimentally in choline deficiency.

On the basis of our present knowledge of nutrition, choline therapy would be indicated in the cases reported by Sheldon and Hertig. It is entirely possible that cystine, methionine, and choline are all involved in cases of idiopathic kidney damage.

PYRIDOXINE THERAPY FOR ACNE VULGARIS

Jolliffe, Rosenblum, and Sawhill (*J. Invest. Dermat.* **5,** *143 (1942)*) report beneficial results from the treatment of persistent adolescent acne with pyridoxine (vitamin B_6). They appear to have been led to a trial of pyridoxine therapy for this disease through a number of considerations, paramount among which is the characteristic frequency of skin lesions in deficiency states arising from the lack of several members of the vitamin B-complex, i.e., riboflavin, niacin, and pyridoxine. No mucous membrane or skin lesions have been described for pyridoxine deficiency in man. However, rat acrodynia, the characteristic dermatitis of pyridoxine deficiency in the rat, is associated with seborrheic lesions and may be the analogue of certain seborrheic diseases in man.

Further reasons given by the authors for the selection of pyridoxine, rather than riboflavin or niacin, include the studies of Gross (*Arch. Dermat. Syph.* **43,** *504 (1941)*). Gross obtained good results with crude liver extracts in the treatment of a variety of cutaneous eruptions but was unable to duplicate the effect of the whole vitamin B-complex with pure niacin or riboflavin. Another reason was their own observation that the "dyssebacia" present in many of their patients with pellagra and ariboflavinosis usually responded to diets rich in the B-complex but not to pure thiamine, niacin, or riboflavin. The work of Birch (*J. Biol. Chem.* **124,** *775 (1938)*) suggests that the physiologic function of pyridoxine may be connected with the utilization of the unsaturated fatty acids. Thus, pyridoxine

may be of benefit in acne through a corrective action on a deranged fatty acid or lipid metabolism.

Jolliffe and co-workers treated an initial group of 10 college freshmen, ages 17 to 23 years, with daily doses of pyridoxine, for periods of one to eleven months. All 10 improved and 3 cleared completely. Improvement was maintained in 4 subjects when the pyridoxine therapy was discontinued. The relapses, which occurred when the therapy was discontinued in the other 6 subjects, were corrected when pyridoxine therapy was reinstituted.

In a second study, 72 subjects, ages 16 to 29 years, were used. Thirty-seven were treated with pyridoxine and 35 with tablets of starch and sugar. The treatment period is not definitely stated but it appears to have been not less than 4 months in any case. The duration of the acne, prior to treatment, varied from one to ten years. Aside from the acne, all subjects were in good health.

Nine of the treated cases cleared completely while none of the control group showed a complete remission. Nineteen of the treated group and 7 of the controls improved. Six of the treated and 19 of the control group remained unimproved. Three of the first and 9 of the second group dropped out of the study.

In many of the subjects treated with pyridoxine a marked reduction in the oiliness of the skin, even in some cases to the point of actual dryness and scaling was noted, independent of the effect on the acne.

The authors conclude that the effective oral doses varied from 50 to 250 mg. daily in divided doses, whereas it would appear from their tables that a daily dose of 20 mg. (5 mg. q.i.d.) proved effective in 3 cases and 30 mg. in one case. "Generally it took seven to ten days of continued administration of the effective doses of vitamin B_6 to obtain definite improvement; although in one case, remissions or exacerbations could be observed in as short a time as three days."

Adolescent acne is subject to apparently spontaneous remissions and relapses and seasonal variations. It generally tends to clear as the period of adolescence is left behind, although there are many cases which are notoriously persistent and resistant to the ordinary forms of therapy. Occurring as it does at a period of life when emotional stability and mature judgment are far from the rule, it is often the cause of considerable unhappiness and, in some cases, of definite psychiatric disturbance. Permanent disfiguring, pitting, and scarring often remain when the acne subsides. Thus the prevention and cure of this disease must be considered prime medical problems. (They have for many years provided the livelihood of numerous quacks and manufacturers of patent medicines.) As the work of Jolliffe and co-workers indicates a reasonable possibility that pyridoxine therapy may be effective in many cases, this form of treatment would appear to deserve adequate trial by other clinical investigators. However, one must caution against the wide acceptance of pyridoxine as the best treatment without the confirmation of more controlled experiments. Hope was aroused by the early experiments with hormonal therapy for acne but this treatment failed to justify itself in further controlled experiments.

NOTES

Nutrition Reviews Coverage

Many readers of NUTRITION REVIEWS will be interested to know that over 100 selected publications are regularly assigned for coverage by our editorial staff. These include practically all of the journals that carry research papers related to nutrition.

Letters to the Editor

Dear Sir:

Your article, "Industrial Nutrition and the War" published in the January, 1943, issue of Nutrition Reviews is mainly a review of my paper in The American Journal of Public Health (**32**, May, 1942). It contains omissions which give an erroneous impression and which I feel it will be useful to correct. I therefore trust you will publish this letter. My paper was a condensation of a speech read on May 25, 1941. The date *is* important. It was prior to the National Nutrition Program and one of its purposes was to interest Public Health Officers in California in nutrition as a public health responsibility.

Commenting on an example cited of rats protected from the deleterious effects of noise by vitamins of the B complex, you make the, I think, gratuitous criticism, "Anatomically and functionally there is a considerable difference between the nervous system of the rat and that of man." Apparently you overlooked the succeeding paragraph of mine: "It will be interesting to ascertain whether workers exposed to a great deal of noise require more than ordinary amounts of the vitamin B complex."

Your comment on my reference to the findings in Stiebeling and Phipard's well known survey is again a combination of the gratuitous and of trying to have it both ways. You write: "But one should also bear in mind that the survey . . . did not attempt to find out whether the 65 per cent on 'bad' diets were in poorer health than those on better diets. That question remains to be answered."

It does; the Committee on Nutrition in Industry of the National Research Council is endeavoring to obtain the answer. Discussing this need at length, I wrote: ". . . that it is of the highest importance for public health nutrition that where measures such as these are taken (use of vitamin concentrates as supplements), the results of these measures be carefully recorded and studied. . . . We must be on our guard against extravagant statements and promises of what will be achieved. There can be no doubt that improvement in the health of the workers as a result of improved nutrition will be beneficial; but the particular respects in which these benefits will manifest themselves in this country remain to be demonstrated."

But why did you write earlier in your review: "Undoubtedly improving the nutrition of our workers (and of other individuals) who do not receive adequate food would result in improved health and greater output of work"?

You accuse me of being "perhaps intentionally more stimulating than conservative." Is the last sentence of yours I have cited a sample of your conservatism? While it is debatable whether conservatism is appropriate on all occasions, there is no debate on the desirability of consistency in an editorial review.

In your insistence that many of the signs and symptoms of malnutrition may be caused by other diseases, you stressed cancer as one of them. You apparently overlooked, on the one hand, that my audience consisted exclusively of medical officers; and on the other hand, that explicit reference (a whole paragraph in the paper) was made to the limits of what can be expected from improved nutrition.

You inferred from my description of some of the difficulties to be overcome by anyone attempting at that time—May, 1941—to improve the meals served in factories that I am "sympathetic with the widespread administration of synthetic vitamins and vitamin concentrates to industrial workers." There is nothing in my paper to justify such a conclusion, especially by a "conservative" reviewer. As a matter of fact, I am not sympathetic to the widespread use of synthetic vitamins and vitamin concentrates in factories in place of a good meal. Nothing can take the place of a good meal except a good meal. What I did say was: "Food preparations containing synthetics or concentrated vitamins can be valuable supplements to even a good diet, and even more to diets which are restricted for whatever reason."

Restriction of highly nutritious foods is with us now and the canonical justification for the use of synthetic vitamins to supplement diets under these circumstances is contained in a quotation cited from a release of the National Research Council: ". . . There is ample reason to believe that any population receiving a diet fully adequate in vitamins, minerals, and other nutritive essentials is better able to withstand the stresses and

strains of war . . .;" and in my paraphrase of a National Research Council Release, "the National Research Council emphasized that synthetic vitamins are identical in every respect—chemically, nutritionally, and medically—with those in foods."

As a matter of fact, the purpose of my remarks on the use of synthetic vitamins and vitamin concentrates (and that purpose is plain in the paper) was to win the support of Health Officers in California to the enrichment of bread and flour, which had not yet become National Nutritional Policy (it was May, 1941) and to meet the arguments of the diehard nutritionists, dietitians, and home economists opposed to it.

H. Borsook
Professor of Biochemistry
California Institute of
January 22, 1943 Technology

Dear Sir:

I believe it is only fair that you should have the expressions of opinions by readers of . . . Nutrition Reviews. I am glad to report that . . . most of our workers, older and younger, are agreed that the Reviews far exceeds their expectations. The one outstanding accomplishment . . . is in the aspect of truly critical assessment . . . Furthermore, the articles are not mere summaries but . . . present very intelligent correlations of experimental results and theories from various sources . . . We wish Nutrition Reviews continued success and an increasing sphere of usefulness and stimulation to the progress of our science.

W. A. Perlzweig
Professor of Biochemistry
Duke University School of
February 2, 1943 Medicine

Enriched Bread

To safeguard the nutritional value of white bread, order No. 1 of the Food Distribution Administration, which became effective January 18, 1943, provides that all white bread must be enriched to approved nutritive standards. This is a most important and desirable order and will do much to improve the nutritional quality of our diet. It is to be hoped that improvement in milling procedures will be vigorously pursued so that flours of light color and good keeping quality and yet of superior nutritional standards will become available.

Army Standards for Dehydrated Foods

The Quartermaster's Corps has issued tentative specifications for dehydrated cabbage, carrots, and onions. These specifications cover in detail such topics as preparation, blanching, dehydration, quality standards, rehydration, and packaging. These and previous standards for dehydrated white potatoes, sweet potatoes, rutabagas, and beets have been conveniently summarized. *Food Industries* **15,** *55 (1943)*; *Ibid.* **14,** *54 (1942)*).

Restaurant Food

The National Nutrition Program, directed largely to the general consumer, is now beginning to affect restaurants and public eating places. In general, the proprietors of public eating places have been conservative toward the idea of nutrition, feeling that it was their job to "give the people what they want," and not attempt to guide their food selection. Even the word "nutrition" has been anathema. Many of the leading restaurants, of course, have sought to put into their operating practices the elements of proper food preparation and good food selection in menu planning. Since the National Nutrition Conference in May, 1941, the educational department of the National Restaurant Association has sought to introduce nutritional concepts into the thinking of restaurant operators.

In recent months the industry has taken definite steps toward formal cooperation with the National Nutrition Program. A nutrition committee of the National Restaurant Association met with representatives of the Nutrition Division, Office of Defense Health and Welfare Services and agreed that the principal points to stress in restaurant nutrition were the importance of food preparation methods so as to retain a maximum of nutritive elements, and secondly, to make menu planning reflect the twin objectives of food conservation and nutritionally adequate meals.